PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X 16/4/17

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/025592	25.08.2004	27.08.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/138, A61K31/5375, A61K31/4468, A61K31/538, A61K31/5415, A61K31/40, A61K31/4025, A61K31/445,

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/025592

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-6 (partially)

because:

☒ the said international application, or the said claims Nos. 1,3-6 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-6 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-6 (all partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4
	No:	Claims	1-3,5-6
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-6
Industrial applicability (IA)	Yes:	Claims	2
	No:	Claims	1,3-6 (see separate sheet)

2. Citations and explanations

   see separate sheet

Re Item III.

1. Claims 1 and 3-6 (as far as relating to the method of treatment) relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. In reply to the objection to lack of unity, the applicant has not paid additional search fees. The international search report has been established for the first invention only.

No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item IV.

The separate inventions/groups of inventions are:

1. claims: 1-6 (all partially)
Use of atomoxetine or a compound of formula (I) for treating a learning disability

2. claims: 1-5 (all partially)
Use of racemic reboxetine or (S,S) reboxetine for treating a learning disability

3. claims: 1-5 (all partially)
Use of a compound of formula (IA) for treating a learning disability

4. claims: 1-5 (all partially)
Use of a compound of formula (IB),(IC) or (IG) for treating a learning disability

5. claims: 1-5 (all partially)
Use of a compound of formula (ID) for treating a learning disability

6. claims: 1-5 (all partially)
Use of a compound of formula (IE) for treating a learning disability

7. claims: 1-5 (all partially)
Use of a compound of formula (IF) for treating a learning disability

8. claims: 1,2,6 (all partially)
Use of atomoxetine or a compound of formula (I) for treating a Motor Skills Disorder

9. claims: 1,2 (all partially)
Use of racemic reboxetine or (S,S) reboxetine for treating a Motor Skills Disorder

10. claims: 1,2 (all partially)
Use of a compound of formula (IA) for treating a Motor Skills Disorder

11. claims: 1,2 (all partially)
Use of a compound of formula (IB),(IC),(IG) for treating a Motor Skills Disorder

12. claims: 1,2 (all partially)
Use of a compound of formula (ID) for treating a Motor Skills Disorder

13. claims: 1,2 (all partially)
Use of a compound of formula (IE) for treating a Motor Skills Disorder

14. claims: 1,2 (all partially)
Use of a compound of formula (IF) for treating a Motor Skills Disorder

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem to be solved by the present invention is to provide a medicament for treating a learning disability or a Motor Skills Disorder.
The proposed solution is to use a norepinephrine reuptake inhibitor selected from:
1. atomoxetine or a compound of formula (I)
2. racemic reboxetine or (S,S) reboxetine
3. a compound of formula (IA)
4. a compound of formula (IB),(IC), or (IG)
5. a compound of formula (ID)
6. a compound of formula (IE)
7. a compound of formula (IF)

The norepinephrine reuptake inhibiting property, represents the technical feature which may, a priori, unify the different compounds 1 to 7 for each of the disorders claimed.

However, the use of norepinephrine reuptake inhibitors for treating a learning disability and a Motor Skills Disorder has been already described in the state of the art.

WO02053104 discloses the use of norepinephrine reuptake inhibitors (e.g. reboxetine) for treating memory impairment such as learning disabilities (see page 2, line 20 to page 3, line 33; claims 1-15).

Atomoxetine is a known norepinephrine reuptake inhibitor which enhances cognitive function and can be used in patients who have problems with working memory (XP8038406).

Atomoxetine (tomoxetine) is also described as a learning enhancer in WO02078629 (see page 6, lines 25-30; claims 1,4-6).

The use of norepinephrine reuptake inhibitors (including atomoxetine) for treating motor inefficiency or for increasing the efficiency of motor learning is disclosed in DE10244537.

Consequently, because norepinephrine reuptake inhibitors have been already disclosed for treating a learning disability and a Motor Skills Disorder in the state of the art (see the various references mentioned above), the norepinephrine reuptake inhibiting property can no longer serve as a single general inventive concept linking the different compounds 1 to 7 for each of the disorders claimed.

Therefore, the use of the compounds 1 to 7 for treating A) a learning disability and B) a Motor Skills Disorder represents each a distinct invention characterised by its own special technical feature.

In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed above. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution

which each of the claimed inventions, considered as a whole, makes over the prior art.

As the applicant has not had a search report drawn up on the other inventions, the present opinion will be established on the basis of the invention in respect of which a search has been carried out, in other words the first invention.

Re Item V.

1 The following document is referred to in this communication:

Reference is made to the following documents:

D1: STAHL STEPHEN M: "Neurotransmission of cognition, part 2. Selective NRIs are smart drugs: exploiting regionally selective actions on both dopamine and norepinephrine to enhance cognition." THE JOURNAL OF CLINICAL PSYCHIATRY. FEB 2003, vol. 64, no. 2, February 2003 (2003-02), pages 110-111, XP008038406 ISSN: 0160-6689

D2: WO 02/078629 A (DAVIS MICHAEL ; LU KWOK-TUNG (US); RESSLER KERRY J (US); UNIV EMORY (U) 10 October 2002 (2002-10-10)

D3: WO 02/053140 A (PHARMACIA AB ; SVENSSON TORGNY (SE); WONG ERIK HO FONG (US); UPJOHN CO) 11 July 2002 (2002-07-11)

D4: WO 03/049724 A (YANG CHARLES RENKIN ; LILLY CO ELI (US); BYMASTER FRANKLIN PORTER (US)) 19 June 2003 (2003-06-19)

D5: WO 02/053104 A (EPSTEIN MEL H ; SENTION INC (US); WIIG KJESTEN A (US)) 11 July 2002 (2002-07-11)

2 NOVELTY (Article 33(2) PCT)

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1,2,3,5,6 is not new in the sense of Article 33(2) PCT.
The document D1 discloses atomoxetine as a norepinephrine reuptake inhibitor which

enhances cognitive function and which can be used in patients who have problems with working memory.

2.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1,2,3,5,6 is not new in the sense of Article 33(2) PCT.
The document D2 discloses atomoxetine (tomoxetine) as a learning enhancer (page 6, lines 25-30; claims 1,4,5,6).

2.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1,2,3,5,6 is not new in the sense of Article 33(2) PCT.
The document D2 discloses a composition comprising a norepinephrine reuptake inhibitor (tomoxetine) and a neuroleptic for treating an age-associated learning disorder.

3 INVENTIVE STEP (Article 33(3) PCT)

3.1. Should the Applicant have overcome the objections of lack of novelty raised above, an inventive step could not be acknowledged over D1 to D5 as the present subject-matter of claims 1,2,3,5,6, as far as novel, appears to be obvious over said documents (Article 33(3) PCT).
Norepinephrine reuptake inhibitors such as atomoxetine are well known cognitive and/or learning enhancers (see D1 to D5).

3.2 The same applies to the subject-matter of the dependent claim 4 which apparently does not contain any technical features which could be regarded as inventive per se.

4 INDUSTRIAL APPLICABILITY

4.1 There are no doubts about industrial applicability (Art.33(4) PCT) for the subject-matter of claim 2 and claims 3-6, as far as relating to the use for the manufacture of a medicament.

4.2 For the assessment of the present claims 1 and 3-6 (relating to the method of treatment) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially

applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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